Remarks

Claims 9, 11, 12, 14, 23-26, and 44-50 were pending in the application. By this amendment, claims 51-53 are added. Therefore, claims 9, 11, 12, 14, 23-26, and 44-53 are now pending.

Support for the new claims can be found throughout the specification, for example: page 2, lines 19-22 and page 10, lines 27-28. Therefore, no new matter is added by this amendment.

35 U.S.C. § 103(a)

Claims 9, 11, 12, 14, 23-26 and 48-49 are rejected under 35 U.S.C. § 103(a) as unpatentable over Isner *et al.* (WO 98/19712), an article from the Japan Financial Times (December 14, 1998), and Li *et al.*, (U.S. Patent No. 6,066,123) in further view of Morishita *et al.* (EP 0847757). Applicants disagree and request reconsideration.

It is asserted on page 4 of the Office action that at the time of the present invention,

> "short-term expression of a nucleic acid *in vivo* because of the short half-life of HGF and/or nucleic acid, and/or inactivation of the nucleic acid, and/or natural maturation and sloughing off of the transformed cell was well known to one of ordinary skill in the art and several applications (e.g., every few days or every few weeks) of the nucleic acid would be required to treat the ischemic disease in the subject."

To support this assertion, Li *et al.* (US 6,066,123, column 8) is referred to. The relevant portion of Li *et al.* states: "In general, gene product expression from the introduced nucleic acid ranges from at least about 1 to 2 days, or 3 to 5 days, to about 1 week, generally about 1 to 4 weeks, up to about 6 weeks, and may be as long as about 10 to 12 weeks or longer." However, Li *et al.* does not particularly discuss HGF gene expression, and instead merely provides a general description about the duration of transgene expression.

It is asserted in the Office action that it would be obvious to administer a nucleic acid encoding HGF every few days or every few weeks to treat lower limb ischemic disease due to the problems associated with delivering nucleic acid *in vivo* (such as the short-term expression of a nucleic acid *in vivo* or the short half-life of HGF and/or nucleic acid). In fact, if one assumes as indicated in the Office action that administration of an HGF nucleic acid would result in only

short-term expression or was unstable, or that HGF has a short half-life, one of ordinary skill in the art would have reasonably expected that the HGF gene administration interval should be short, such as 1 to 2 days. One skilled in the art would not conclude that administration every few weeks would be sufficient. Therefore, the prior art cited teaches away from the administration protocol claimed.

In contrast to this expectation, the present inventors found that administration schedule of once every few days or even once every few weeks is appropriate for HGF gene. Indeed, the instant specification demonstrates that the effect of the HGF gene was maintained even after 3 weeks and 5 weeks after its administration (see FIGS. 3 and 4). Such findings would not have been readily expected from the short half-life of HGF. In addition, administering the HGF gene less frequently lowers costs, therefore providing an unexpected benefit. Therefore, the claims of the present application provide an unexpected superior result over the prior art.

In summary, because the prior art suggests that administration of the HGF gene should be administered more frequently, this teaches away from an administration protocol where the HGF gene is administered less frequently. In addition, such less frequent administration provides an unexpectedly superior benefit by lowering costs. Therefore, the claims are not obvious.

It is also asserted that the claimed dosages are unpatentable. Applicants disagree and request reconsideration. The claims specify that at least 50μg of HGF gene is administered. Although Morishita *et al.* disclose 0.1 to 100,000 μg (0.0001 mg to 100 mg), preferably 1 to 10,000 μg (0.001 mg to 10 mg), these ranges cover a range over 10,000-fold,to 1-million-fold thus not particularly indicating to one skilled in the art what dosage should be used. This language indicates that the guidance in Morishita *et al.* is prophetic and simply provides general guidance or acceptable means of administration in a therapeutic setting, and is not specifically directed towards administration of HGF gene for treatment of diabetic ischemic disease. Furthermore, determining which dosages would provide the desired therapeutic effect within such a wide range of dosages requires a significant amount of experimentation by one skilled in the art. Therefore, beyond routine experimentation was required to determine an appropriate dose of HGF gene to administer for treating diabetic ischemic disease. As a result, MPEP 2144.05 does not apply.

The instant specification discloses, angiogenesis hardly occurs and prognosis is unfavorable in ischemic disease complicated with or caused by diabetes (see page 2, lines 23-

25). The present application clarifies one of the reasons for these unfavorable events in diabetic ischemic disease. The instant specification shows that endogenous HGF in the diabetic lower limb ischemic disease model is much lower than that of control (see page 11, lines 7-30). Based on this observation, the HGF gene dose recited in the instant claims was determined. In other words, without knowing that endogenous HGF in the diabetic lower limb ischemic disease model is much lower than that of control, one skilled in the art would not have been motivated to determine an appropriate dose of HGF gene for treating diabetic ischemic disease. Therefore, an appropriate dose of HGF gene would not have been determined. Therefore, one skilled in the art would not have been motivated to determined the HGF gene dose to treat diabetic ischemic disease.

Claims 44-47 and 50 are newly rejected under 35 U.S.C. §103(a), as allegedly being unpatentable over Isner *et al.* (WO 98/19712) in combination with an article from the Japan Financial Times (December 14, 1998) in further view of Morishita *et al.* (EP 0847757). Applicants disagree and request reconsideration. As noted above, a dosage of at least 50 μg is not obvious, and therefore the claims are patentable in view of the prior art cited.

Therefore, the present invention is not obvious, and Applicants request that the 35 U.S.C. § 103(a) rejections be withdrawn, and a Notice of Allowance issued.

If any matters remain before a Notice of Allowance is issued, the Examiner is invited to telephone the undersigned.

Respectfully submitted,

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